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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,955	08/21/2001	Philippe Crine	163-35	5955
23117	7590	12/31/2003		
NIXON & VANDERHYE, PC 1100 N GLEBE ROAD 8TH FLOOR ARLINGTON, VA 22201-4714			EXAMINER RAMIREZ, DELIA M	
			ART UNIT 1652	PAPER NUMBER

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/913,955

Applicant(s)

CRINE ET AL.

Examiner

Delia M. Ramirez

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2 and 6-40 is/are pending in the application.
- 4a) Of the above claim(s) 7-12, 14-19, 22-32 and 35-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 6, 13, 20, 21, 33 and 34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

Claims 2, 6-40 are pending.

Applicant's amendment of claims 2, 6, 13, 20-21, 33, cancellation of claims 1, 3-5, and amendments to the specification, in a communication filed on 9/30/2003 are acknowledged.

This application contains claims 7-12, 14-19, 22-32, 35-40 drawn to an invention non-elected with traverse in Paper No. 9, filed on 10/2/2002. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2, 6, 13, 20-21, 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
3. Claim 2 (claims 6, 13, 20-21, 33-34 dependent thereon) is indefinite in the recitation of "a soluble purified(secPHEX) wherein the amino acid residues located from position 27 to position 46 inclusively according to the numbering used in the sequence of SEQ ID NO: 1 have been replaced by the amino acid residues of SEQ ID NO: 4" for the following reasons. Applicants state in the Remarks section of the Response filed on 9/30/2003 that reference to SEQ ID NO: 1 is only to indicate which residues are to be substituted to create a soluble PHEX and that the present invention is not in any way limited to a particular sequence for PHEX other than that of SEQ ID NO: 4. It is noted however that the claim as written appears to indicate that the claimed secPHEX protein has the amino acid sequence of

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SEQ ID NO: 1 except for the substitution of amino acids 27-46 with those amino acids of SEQ ID NO: 4. For examination purposes, it will be assumed that the claim is directed to "any soluble purified phosphate regulating gene with homologies to endopeptidases on the X chromosome enzyme wherein the amino acid residues corresponding to position 27 to position 46 of the polypeptide of SEQ ID NO: 1 have been replaced by the amino acid residues as set forth in SEQ ID NO: 4". Correction is required.

4. Claim 6 (claim 21 dependent thereon) is indefinite in the recitation of "a mutant of the secPHEX of claim 1" as claim 1 is now cancelled. For examination purposes, it will be assumed that the claim is directed to the secPHEX protein of claim 2 (as interpreted above) wherein a glutamic acid residue corresponding to position 581 in the polypeptide of SEQ ID NO: 1 has been substituted with a valine residue. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

5. Claims 2, 6, 13, 20-21, 33-34 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This rejection has been discussed at length in Paper No. 14, mailed on 6/18/2003.

7. Applicants argue that claims 3-5 have been cancelled and claim 6 is specifying that the residue at position 581 according to the numbering used in the sequence of SEQ ID NO: 1 is valine. Applicants also submit that claim 1 has been cancelled and the remaining claims were amended to accelerate prosecution.

8. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. While the Examiner acknowledges the amendment of claims 2, 6, 13, 20-21, 33 and cancellation of claims 1, 3-5, as indicated above under Claim Rejections under 35 USC 112, second

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paragraph, in view of Applicant's remarks, claim 2 has been interpreted as being drawn to a genus of soluble purified PHEX proteins wherein the amino acid residues corresponding to position 27 to position 46 of the polypeptide of SEQ ID NO: 1 have been replaced by the amino acid residues as set forth in SEQ ID NO: 4. Claim 6 as interpreted above is directed to the genus of PHEX enzymes of claim 2 with the added limitation that a glutamic acid residue corresponding to position 581 has been substituted with a valine residue. As such, the claims encompass any PHEX which has been modified as recited in the claims. It is reiterated herein that the specification is silent in regard to the structure of other PHEX enzymes, as encompassed by the claims from other sources, including other human or murine PHEX enzymes. No disclosure of the critical structural elements required in a polypeptide to display PHEX function has been provided either. Furthermore, the specification fails to disclose which are the residues in any PHEX enzyme which correspond to amino acids 27-46 or 581 of SEQ ID NO: 1. As indicated previously, an adequate description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. In the instant case, no structural features are recited and the specification does not provide the structural features necessary for members of the genus to be selected. The specification only discloses a single species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera required to practice the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 2, 6, 13, 20-21, 33-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) the human PHEX enzyme of SEQ ID NO: 1 which has been modified such that amino acids 27-46 have been replaced with the amino acids of SEQ ID NO: 4 to

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increase solubility, and (2) an inactive human PHEX enzyme variant of the polypeptide of SEQ ID NO: 1 or that of (1) which has been modified to replace the glutamic acid residue of position 581 of SEQ ID NO: 1 with a valine residue, does not reasonably provide enablement for (1) any PHEX enzyme which has been modified such that those amino acids corresponding to amino acids 27-46 of SEQ ID NO: 1 have been replaced with the amino acids of SEQ ID NO: 4 to increase solubility, or (2) any inactive PHEX enzyme which has been modified such that the glutamic acid residue corresponding to position 581 of SEQ ID NO: 1 has been replaced with a valine residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. This rejection has been discussed at length in Paper No. 14, mailed on 6/18/2003.

11. Applicants argue that claims 3-5 have been cancelled and claim 6 is specifying that the residue at position 581 according to the numbering used in the sequence of SEQ ID NO: 1 is valine. Applicants also submit that claim 1 has been cancelled and the remaining claims were amended to accelerate prosecution.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. As indicated above, the claims are now directed to any PHEX enzyme comprising the limitation recited in the claims and the specification fails to disclose (1) the structure of other PHEX enzymes, (2) which are the amino acids in any PHEX enzyme which correspond to amino acids 27-46 or 581 of SEQ ID NO: 1, or (3) how to isolate other PHEX enzymes in the absence of any information as to the critical structures required in any polypeptide to display PHEX activity. In addition, as indicated previously, the state of the art teaches the unpredictability of determining function based solely on structural homology. See the teachings of Bork, Witkowski et al., Van de Loo et al., Seffernick et al., and Broun et al. already discussed. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the structural elements required to display the desired

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function, and the unpredictability of the prior art in regard to determining function based on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate all PHEX enzymes as encompassed by the claims and (2) determine which residues in those PHEX enzymes correspond to amino acids 27-46 or 581 of SEQ ID NO: 1. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. Claims 2 and 13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (Journal of Bone and Mineral Research 12(7):1009-1017, 1997; cited in previous Office Action Paper No. 8) in view of Lemire et al. (Biochem. J. 322:335-342, 1997; cited in the IDS).

15. Claims 33-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (Journal of Bone and Mineral Research 12(7):1009-1017, 1997; cited in previous Office Action Paper No. 8) in view of Lemire et al. (Biochem. J. 322:335-342, 1997; cited in the IDS), as applied to claims 1 and 2 above, and further in view of Ni et al. (U.S. Patent No. 5840509, November 24, 1998).

16. Amended claims 2 and 13 are now directed to a soluble PHEX enzyme wherein the amino acids corresponding to positions 27-46 of SEQ ID NO: 1 have been replaced with the amino acids set forth in SEQ ID NO: 4. Claims 33-34 are now directed to a method of obtaining PHEX ligands by using the soluble PHEX enzyme of claim 2. Since neither Guo et al., Lemire et al., or Ni et al., individually or in combination, teach the claimed invention, this rejection is hereby withdrawn.

Conclusion

17. No claim is in condition for allowance.
18. Applicant's amendment of claims 2, 6, 13, 20-21, 33 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

19. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED**, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
December 15, 2003

Delia M. Ramirez
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